Issues within Keratinocyte Growth Factor (KGF) research

ZHENG Wen-jing[1], YUAN Li[3], LIU Xue-dong[1,2], ZHENG Dong*

[1] *Laboratory of Genetics and Molecular Biology, College of Wildlife Resources, Northeast Forestry University, Harbin, 150040, China*

[2] *Laboratory of Genetics Resources, Institute of Animal Science, Chinese Academy of Agricultural Sciences, Beijing, 100094, China*

[3] *School of Forestry, Northeast Forestry University, Harbin, 150040, China*

Abstract: As the seventh member of Fibroblast Growth Factor (FGF) family, Keratinocyte Growth Factor (KGF or FGF-7) is observed to mediate epithelial cell proliferation and differentiation in a variety of tissues. In this article, such following issues within KGF research were reviewed, as (1) KGF functioning pathways: experimental results demonstrated the paracrine pathway of KGF played main role in mesenchymal-epithelial interactions whereas KGF itself was under the control of a feedback regulation, autocrine provided KGF alternative functioning way particularly in tumourogenesis; (2) KGF in apoptosis: a few of investigations recently illustrated KGF mediated cell survival was based on its mitogenic function via stimulating cell growth, moreover KGF could inhibit the ROS-induced apoptosis through Nrf-2 pathway; (3) KGF during tumourogenesis: high expression of KGF enhanced progression, motility and invasiveness of tumor cells and various cancers, in company with paracrine loop replaced by autocrine loop, meanwhile KGF clearly played the early signal in the progression of breast cancer; (4) Medical application and administration of KGF: KGF had been successfully used in several preclinical models of radiation and chemotherapy-induced mucositis, and developed into commercial medicine (i.e. Palifermin), however more effective delivery systems are still under trial.

Keywords: Keratinocyte Growth Factor (KGF or FGF-7); Paracrine; Autocrine; Apoptosis; Tumourogenesis; Medical administration

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Introduction

Keratinocyte growth factor (KGF or FGF-7) is the seventh member of Fibroblast Growth Factor (FGF) family. Initially it was isolated and identified from M426 human embryonic lung fibroblasts 16 years ago (Finch *et al.* 1989), and usually functions as a 26-28 kD polypeptide. Until now, such cells as mesenchymal cells, activated γδT cells and CD8-positive T lymphocytes have been found to be able to produce KGF (Boismenu & Havran 1994; Wei *et al.* 2005). As local growth factors, all the members of the FGF family share several subtypes of FGF-receptors (FGFR), which mediate biological effects by heparin and heparan sulfate proteoglycans (Johnson & Williams 1993; Ornitz & Itoh 2001), and KGF binds exclusively with one isoform, known as FGFR2IIIb (Ornitz *et al.* 1996; Steiling *et al.* 2003).

KGF is observed to mediate epithelial cell proliferation and differentiation in a variety of tissues. For example, Galiacy *et al.* (2003) confirmed KGF played a key role in lung epithelial repair through several mechanisms involved in cell migration and protected against various injuries. Also KGF has the potential to protect the thymic epithelium and protect or restore thymic damage after chemo/radiotherapy (Alpdogan *et al.* 2005). Being inhibit the apoptosis through promoting the cell proliferation, the ability of KGF to ameliorate severe oral mucositis (OM) that results from cancer chemoradiotherapy had been evaluated. Similar studies showed KGF significantly reduced both the incidence and duration of severe OM (Finch & Rubin 2004).

KGF functioning pathways: paracrine *vs.* autocrine

It has been well-known that KGF is produced by mesenchymal cells (i.e. fibroblasts) (Werner 1998; Beer *et al.* 2000), and KGF acted through paracrine pathway, enhancing keratinocyte migration and proliferation, as well as protective effects against γ-irradiation and reactive oxygen species (Gillis *et al.* 1999; Michelson *et al.* 1999; Andreadis *et al.* 2000; Slonina *et al.* 2001; Karvinen *et al.* 2003). Werner (1998) investigated the expression pattern of KGF and its receptor on mouse wound model through *in situ* hybridization and immunohistochemical staining of the wound tissue, and determined the presence of KGF mRNA in dermal fibroblasts below the wound and at the wound edge whereas the presence of KGF receptor transcripts and the corresponding protein in keratinocytes of the epidermis (Werner *et al.* 1992; Werner 1998). Hovey *et al.* (2001) investigated the role of KGF during epithelial–stromal interactions accompanying ruminant mammogenesis. Their results supported the paracrine role of KGF. Moreover, experiments on the effect of smokeless tobacco (ST) on HGF, KGF and GM-CSF expression by buccal fibroblasts and on keratinocyte and fibroblast proliferation, suggested that HGF and KGF may play an important role as a paracrine growth factor in epithelial hyperplasia in ST lesions (Dabelsteen *et al.* 2005).

It should be noticed that KGF itself is under the control of a feedback loop. After injury, polymorphonuclear leukocytes and macrophages that produce pro-inflammatory cytokines (including IL-1) could infiltrate the wound. By analyzing the temporal and spatial expression of these cytokines during cutaneous wound repair, it was determined that the time-course of expression of these cytokines after injury correlated with the time-course of KGF expression and polymorphonuclear leuko-

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Biography: ZHENG Wen-jing (1982-), female. Graduate of Physiology in College of Wildlife Resources, Northeast Forestry University, Harbin, 150040, China. Email:wenjingzheng@yeah.net

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* Correspondence. Email:zhengdong@nefu.edu.cn

cytes, macrophages and keratinocytes co-localized with the fibroblasts in the early wound. This study demonstrated pro-inflammatory cytokines (including IL-1) could upregulate expression of KGF in the fibroblasts of the wound tissue (Werner *et al.* 1992; Werner 1998; Groves & Schmidt-Lucke 2000; Werner & Smola 2001). Recent investigation further showed that keratinocytes could regulate the expression of KGF in fibroblasts through the release of interleukin-1beta (IL-1β), as a pro-inflammatory molecule that increases fibroblast proliferation and extracellular matrix production, though the effect of solid substrate on the paracrine relationship between keratinocytes and fibroblasts as modulated by KGF and IL-1β is still unclear. By using an *in vitro* skin equivalent model, it was also found that during this mesenchymal-epithelial cross-talk process, transcription factors regulate the expression of interleukin-1 (IL-1)-induced KGF and GM-CSF in fibroblasts (Witte & Kao 2005). These results above clearly demonstrated, during the re-epithelialization of wounded skin KGF provides important signals for interactions between epidermal–dermal cells.

However a few experiments disclosed autocrine could be alternative choice for KGF function. McGarvey & Stearns (1995) firstly examined the expression of keratinocyte growth factor (KGF) and its receptor in normal, fetal, and prostate cancer cells. In both fetal (n = 6) and normal adult prostate (n = 6) tissues examined, the KGF and KGF receptor genes were faintly expressed in the stromal and epithelial cells, respectively. In 10 benign prostatic hyperplasias (BPH), and in low- and high-grade prostatic carcinoma (32 total), both the KGF gene and the receptor mRNA were expressed in the glandular epithelial cells. KGF was also expressed by the stromal cells in BPH and low-grade carcinoma. The computer analysis of the data declined that the paracrine loop in normal prostate may be replaced by an autocrine loop in BPH and adenocarcinomas. In another study, Siddiqi *et al.* (1995) used reverse transcriptase polymerase chain reaction (RT-PCR) to determine whether KGF is expressed in human pancreatic cancers. 44% pancreatic cancer samples revealed significant overexpression of KGF mRNA transcript by comparison with the normal pancreas. Furthermore, 5 of 7 tested cell lines expressed the KGF receptor, and the growth of one cell line was enhanced by human recombinant KGF. These results suggested that KGF may participate in aberrant paracrine and autocrine pathways in human pancreatic cancer. Observations from the investigation of the expression and action of KGF in normal ovarian surface epithelium (OSE) and ovarian cancer tissue indicated that normal OSE expressed high levels of KGF *in vivo* and *in vitro*. Expression of KGF by normal epithelial cells versus stromal cells was unexpected and suggested KGF may be an important autocrine stimulator of OSE (Parrott *et al.* 2000; Parrott *et al.* 2001).

Taken altogether, both paracrine and autocrine pathway may be important for the action of KGF in normal tissues, and in the most cases the action of KGF via the autocrine pathway usually could not be observed. The facts determine that the expression level of KGF by epithelial cells is high in some cancer tissues and the autocrine loop may be enhanced due to hyperplasias or tumourigenesis. However the detailed mechanisms remain to be determined.

Roles of KGF in apoptosis

KGF increases epithelial cell growth (Carrington & Boulton 2005), however, little is known of its effect on apoptosis. A recent study by Wildhaber *et al.* (2003) using C57BL/6J mice model determined the effect of recombinant human KGF (rHuKGF) on small bowel EC apoptosis. Total parenteral nutrition (TPN) - induced apoptosis was associated with decreased Bcl-2 (major mediators of epithelial cell apoptosis) mRNA expression. rHuKGF decreased TPN-induced EC apoptosis and increased Bcl-2 expression. Such results might imply that the rHuKGF administration may have benefit in patients on TPN. Furthermore, there previously had reports that KGF could be a potent mitogen for BPH stromal cells via stimulation of cell growth and inhibition of apoptosis, and KGF accordingly might be involved in the pathogenesis of BPH (Crescioli *et al.* 2002.).

Free radicals, particularly reactive oxygen species (ROS), have been proposed as common mediators for apoptosis. ROS may change cellular redox state, and the abnormal redox state may disrupt signal transduction pathways which results in cell death as opposed to proliferation (Haddad 2004). Previous results from Werner's laboratory suggested that KGF may induce the expression of enzymes involved in the detoxification of ROS. And they had identified several target genes to support their hypothesis. Thereinto, expression of target genes encoding peroxiredoxinVI and NF-E2-related factor 2 (Nrf-2) should be correlated with induction of KGF. The enzyme peroxiredoxin VI can detoxify hydrogen peroxide and organic peroxides (Hofmann *et al.* 2002). Upregulation of peroxiredoxin VI by KGF induced the ROS resistance of keratinocytes (auf dem Keller *et al.* 2004) and interrupted the ROS-induced apoptosis. Additionally, Nrf-2, as a transcription factor, activated various cytoprotective genes encoding ROS-detoxifying enzymes and other anti-oxidative proteins, and also expressed at high levels because of KGF induction in keratinocytes of the wounded epidermis (Braun *et al.* 2002). Therefore KGF could inhibit the ROS-induced apoptosis through upregulation of Nrf-2 and enhancement of detoxification of ROS.

Function of KGF during tumourogenesis

We have known that growth factors influence the progression, motility and invasiveness of tumor cells (Nguyen *et al.* 2002). Evidences continuously suggested that KGF be involved in tumourgenesis of various cancers such as breast, prostate, and human pancreatic cancer (Siddiqi *et al.* 1995; Velagaleti *et al.* 2003). McGarvey & Stearns (1995) disclosed KGF may play a role in the growth of adenocarcinomas, and the analysis further meant that the paracrine loop in normal prostate may be replaced by an autocrine loop in BPH and adenocarcinomas. In addition, KGF is expressed in human pancreatic cancers, and may participate in aberrant paracrine and autocrine pathways in human pancreatic cancer (Siddiqi et al. 1995). The majority of ovarian tumors are derived from the single layer of OSE, in view of KGF being a mitogen specific for epithelial cells, it seems to imply that KGF directly or indirectly influences the progression of ovarian tumors, and this hypothesis had been verified. Gonadotropin actions on the OSE had been postulated to be a potential factor in the onset and progression of some ovarian cancers. Interestingly, the actions of FSH and LH to promote OSE growth may in part be mediated indirectly through an elevation in the expression of autocrine growth factors (KGF, HGF, and kit ligand/stem cell factor (KL)) (Parrott *et al.* 2001).

The KGF signal pathway may be correlated with the local production of estrogen in human breast cancer cell lines. Considering this, some researchers used RT-PCR to study the local ex-

pression of mRNAs for aromatase cytochrome P-450, the enzyme which catalyzes estrogen synthesis, and the local expression of KGF in breast tumors. The results indicated that a high proportion of breast tumors have the potential to produce aromatase and KGF, both of which could play important roles in their growth (Koos *et al.* 1993). The study on conditioned media from NIH 3T3 cells (mouse fibroblast), which contains KGF, implied KGF could increase the motile morphology of estrogen receptor (ER)-positive breast cancer cells and produce no effect on ER-negative cells. Later other studies examined the influence of human KGF on two estrogen receptor (ER)-positive human breast cancer cell lines (MCF-7 and T-47D) and observed that KGF enhanced the migration and proliferation of both MCF-7 and T-47D breast cancer cells. Furthermore, their responses to KGF were found to be both dose- and time-dependent. These studies demonstrated that human KGF enhanced the migration and proliferation of human breast cancer cells, and supported the concept that KGF may be an early signal in the progression of breast cancer to a more motile and metastatic phenotype (Nguyen et al. 2002).

Medical application and administration of KGF

Epidermal regeneration is a complex process in which residual epithelial cells proliferate to reconstitute an intact epidermis (Kanzler *et al.* 1986; Steenfos 1994). The upregulation of KGF expression upon skin injury was thought to be important for wound reepithelialization, since exogenous KGF strongly stimulated this process in animal models (Abraham & Klagsbrun 1996). In addition to its mitogenic function, KGF has been identified as a potent survival factor for different types of epithelial cells in vitro and in vivo (Werner 1998; Finch & Rubin 2004). For example, KGF improved the function of the thymic microenvironment after bone marrow transplantation, resulting in improved immune development and function. Furthermore, it preserved normal thymopoiesis and thymic microenvironment during experimental graft-versus-host disease (Min *et al.* 2002; Rossi *et al.* 2002). Lung epithelial cells were also protected from hyperoxia-induced cell death in the presence of high concentrations of this growth factor (Panos *et al.* 1995; Ray *et al.* 2003; Werner 1998; Finch & Rubin 2004).

Presently, KGF had been successfully used in several preclinical models of radiation and chemotherapy-induced mucositis, a condition characterized by severe ulceration of the oral and intestinal mucosae (Farrell *et al.* 2002). In a phase 3 trial involving patients who were treated with myeloablative chemoradiotherapy before autologous peripheral blood progenitor cell transplantation for hematologic malignancies, KGF significantly reduced both the incidence and duration of severe OM. Similar investigations are underway in patients being treated for solid tumors. On the basis of its success in ameliorating chemoradiotherapy-induced OM in humans and tissue damage in a variety of animal models, additional clinical applications of KGF are still worthy of investigation (Finch & Rubin 2004). The medical name of human-derived KGF (FGF7) is Palifermin, which is injected subcutaneously. A recent study used the mouse models to assess the impact of the administration protocol of Palifermin on amelioration of oral mucositis after fractionated irradiation (Dörr *et al.* 2005). This assessment would be the base of the clinic human treatments in the future.

KGF could be developed for the gene therapy targeting hematopoietic cells. In a study the K-sam gene encoded the receptor for KGF was transduced into the cell lines. The study showed that KGF could efficiently induce proliferation of hematopoietic cells expressing the K-sam gene encoding the receptor for KGF without obvious induction of differentiation or exhaustion of immature progenitor cells. It could overcome the two problems of gene therapy targeting hematopoietic cells: low transduction efficiency and induction of differentiation during cytokine treatment. The *in vitro* data are important for further preclinical *in vivo* study (Kamata *et al.* 2002). Kopp *et al.* (2004) established immortalized HaCaT keratinocytes and KMST-6-fibroblasts stably expressing KGF. Their results indicated that wound healing processes can be stimulated distinctly by growth factors secreted from HaCaT cells, with a prominent role for transgenic KGF.

In vivo study, it was investigated that the electroporation could enhance transfection efficiency and improve wound healing with DNA plasmid expression vectors for growth factors. These results encourage us to explore further the possible benefit of electroporation-facilitated transfection of growth factors to improve wound healing (Lin *et al.* 2004). The another study determined electroporation assisted delivery of KGF expression vector can also improve closure of wounds in diabetic mice model (Marti *et al.* 2004). Reduced proliferative capacity and response to growth factors have been found in aged animal models and electroporation assisted delivery of KGF-1 expression vector restored healing at a rate close to that of young animals. (Marti *et al.* 2004).

By isolating the total RNA and using the RT-PCR, we have recently isolated and cloned the putative gene of KGF (GenBank accession no. AY923858) in the deer velvet tissue in our laboratory. Primary analysis based on alignment and sequences analysis showed there were some specific features within signal domain and N-terminal domain of mature polypeptide (data unpublished). High expression patterns in the deer antler predicted its critical role involved into epimorphic regeneration. Further experiments need to clarify its physic and biochemical characters and biological activities.

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